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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/837,806 | 04/18/2001 | Sudhir Agrawal | HYZ-069CN (47508-407) | 8489 |

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| EXAMINER |
|---|
| ZARA, JANE J |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1635 | |

DATE MAILED: 04/22/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

F-16

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 09/837,806 | Agrawal |
| **Examiner** | **Art Unit** |
| Jane Zara | 1635 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) ☒ Responsive to communication(s) filed on *Jan 31, 2003*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) ☒ Claim(s) *1, 3-16, and 18-39* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3-16, and 18-39* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

This Office action is in response to the communication filed January 31, 2003, Paper No. 9.

Claims 1, 3-16 and 18-39 are pending in the instant application.

Any rejections not repeated in this Office action are hereby withdrawn.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Response to Arguments and Amendments*

Maintained Rejections

Claims 16, 18-30, 34-38 are rejected under 35 U.S.C. 112, first paragraph, for lacking enablement over the scope claimed for the reasons of record set forth in the Office action mailed August 28, 2002, Paper No. 7.

Applicant's arguments filed January 31, 2003 have been fully considered but they are not persuasive. Applicants argue that the claimed invention is enabled because in vitro experiments have demonstrated anti-HIV activity and furthermore that in vivo experiments have demonstrated the bioavailability of the claimed oligonucleotides following oral administration. Contrary to Applicants' assertions, neither the in vitro demonstration of anti-HIV activity, nor the oral bioavailability of oligonucleotides in an organism provide the enablement for the ability to treat and/or inhibit HIV-1 or 2 infection in an organism. In vitro results cannot be extrapolated to in

vivo efficacy. In vivo bioavailability of intact oligonucleotides is not representative of the ability of administered oligonucleotides to reach their appropriate target cells and inhibit or treat HIV-1 or 2 infections in any organism. It would require undue experimentation beyond that which has been provided in the instant disclosure to provide enablement for the ability to treat and/or inhibit HIV-1 or 2 infections in an organism.

Applicants argue further that the claimed invention is enabled because teachings in the art have been disclosed in the instant application which demonstrate the ability of various antisense to successfully target and inhibit the expression of target genes in an organism, and teachings have been disclosed that demonstrate good biological activity, pharmacology and pharmacokinetics in vitro and in vivo for various antisense oligonucleotides, including oligonucleotides comprising various modifications such as phosphorothioated oligonucleotides. Contrary to Applicants' assertions, the ability of one antisense oligonucleotide to successfully bind to and inhibit a target gene is not necessarily representative of the ability of another oligonucleotide to bind to and inhibit a different target gene in an organism. Nor can the efficacy of one molecule be extrapolated to another molecule. The efficacy of that particular molecule must be tested empirically. Furthermore, success using one oligonucleotide with modifications such as phosphorothioate containing oligonucleotides are not necessarily representative or correlative of another modified antisense oligonucleotide. Efficacy depends on various factors, including the target cells harboring the target gene of interest within a particular organism, cellular uptake and target binding of the therapeutic molecule of interest. It would require undue experimentation

beyond that which has been taught in the instant disclosure, and that which has been taught in the prior art, to determine the efficacy of the claimed molecules for the treatment and prevention of HIV-1 or 2 infections in any organism.

Claims 1, 3-15, 31-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al, Goodchild et al and Hovanessian et al for the reasons of record set forth in the Office action mailed August 28, 2002, Paper No. 7.

Applicant's arguments filed January 31, 2003 have been fully considered but they are not persuasive. Applicants argue that the instant invention is not obvious over the combined teachings because, for instance, Agrawal et al in the '721 patent does not explicitly disclose that SEQ ID NO: 1 is complementary to an HIV sequence such as gag. Contrary to Applicants' assertions, the '721 patent discloses, in col. 4, lines 40-54, the motivation to target genes that are of a virus involved in AIDS.... SEQ ID NO: 1 of the '721 patent discloses antisense that specifically target the gag nucleotide sequence, so, although not stated explicitly, the motivation and means to target the HIV gag sequence has been disclosed in the '721 patent.

Applicants argue further that Goodchild et al targets the initiation codon for the gag gene and therefore does not provide motivation appropriate for the instant 103 rejection, nor, according to Applicants, does the Hovanessian et al reference, because it likewise relates to the transmembrane envelope proteins of HIV and not the particular target gene of the instant disclosure. Contrary to Applicants' assertions, both Goodchild et al and Hovanessian et al

provide motivation to target and inhibit known target genes involved in HIV biology and infectivity. Therefore, the motivation provided by these references - using an antisense approach to target and inhibit target genes known to be important and involved in the biology of HIV-1 or 2 (i.e. replication, infectivity...), is appropriate for the instant 103 rejection.

Applicants assert that it would not have been obvious to target regions within SEQ ID NO: 1 of the '721 patent for inhibiting expression of HIV-1 or 2 gag proteins. Contrary to Applicants' assertions, designing shorter antisense within a known target region of a previously disclosed target gene associated with HIV-1 or 2 infectivity would have been obvious. The range of oligonucleotides successfully employed as antisense to target genes of known nucleotide sequence routinely encompass the length of 21 nucleobases. One of ordinary skill in the art would have been motivated to utilize subsequences derived from a known target gene to inhibit the expression of that target gene. This would require routine experimentation. Furthermore, the importance of gag in HIV-1 and 2 biology was well known in the art at the time of the invention, and one of ordinary skill in the art would have expected that subsequences within the previously disclosed gag target sequence would inhibit the expression of gag in vitro and interfere with HIV-1 or 2 infectivity in vitro. Therefore, the instant invention would have been obvious to one of ordinary skill in the art at the time the invention was made.

***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Ram R. Shukla

RAM R. SHUKLA, PH.D
PATENT EXAMINER

*JZ*

April 16, 2003